REMARKS

Claims 1-6 and 8-23 are pending. Applicants amended claim 15 to recite a "method of evaluating the immunological status of a subject by detecting and/or quantifying an IgE antibody specific to a ligand" to make the preamble of claim 15 consistent with the method step recited at the end of the claim. Claim 15 has also been amended to recite the step "obtaining a liquid sample suspected to contain an IgE antibody from the subject." Applicants believe that this amendment of claim 15 does not introduce new matter.

The Office rejects the pending claims under one or more of 35 U.S.C. §§ 112, 102, and 103. Applicants address these rejections below.

Rejection Under 35 U.S.C. § 112

Claim 15 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because, according to the Office, the last step of claim 15 recites "evaluating the immune status of a subject" while the preamble recites a method of detecting IgE antibody. Office Action at page 2.

To facilitate prosecution, Applicants have amended the preamble of claim 15 to recite a "method of evaluating the immunological status of a subject by detecting and/or quantifying an IgE antibody specific to a ligand." This amendment of claim 15 makes the preamble of the claim, "a method of evaluating the immunological status of a subject," consistent with the final step of the claim, "using both the first and the second measurement as a basis for evaluating the immunological status of the subject." Applicants contend that claim 15 is clear and request that the Office withdraw this rejection.

Rejection Under 35 U.S.C. § 102

The Office rejects claims 1-5, 8, 10-12, and 21-23 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent 6,037,453 ("Jardieu"). Office Action at page 3. According to the Office, Jardieu teaches "an assay protocol for IgE antibody, which comprises coating the FcεRI or RII (CD23) on a well plate (carrier)." *Id.* Jardieu allegedly mixes in a separate plate "the sample comprising an MaE11 (anti-IgE) and a reference murine MaE11 monoclonal antibody . . . with a biotintylated IgE (free dissolved ligand)." *Id.*

In order to reject the pending claims, the Office necessarily equates the mixing of MaE11 with biotintylated IgE as the formation of mixture I as recited in the rejected claims and the adding this alleged mixture I to the receptor-coated wells as the formation of mixture II. Id. The Office also alleges that the plate is then washed followed by "adding a substrate to the plate for developing detectable color." *Id.* Both of these are incorrect.

Regarding claims 8 and 10, Jardieu allegedly teaches a chemiluminescent compound covalently bound to streptavidin and a ligand that is bound to biotin. *Id.* at 4. As for claim 15, the Office suggests that Jardieu teaches identifying humanized anti-human IgE antibodies that bind to CD23-bound IgE, but not to FcεRI-bound IgE. *Id.* Applicants traverse this rejection for several reasons.

First, the Office's description of Jardieu's method is incorrect. The assay described in Example 5 at columns 41 and 42 seeks to determine the impact of making changes in the IgE antibody structure on the ability of the variant IgE antibodies to bind to IgE receptors and to an anti-IgE antibody. See Jardieu at col. 41, lines 19-21. In this

assay, the sample is not the MaE11 anti-IgE antibody as the Office suggests, but rather the variant IgE antibodies. The MaE11 anti-IgE antibody in turn may or may not bind to the variant IgE depending on the effect that the mutation has on this binding interaction. Importantly, the IgE variants are not labeled in Jardieu's assay. Rejected independent claims 1, 4, 5, and 21-23 recite "wherein the label to be detected is associated with the ligand or the IgE antibody." Thus, unlike the rejected claims, in Jardieu, the label is not associated with the IgE antibody in the sample. This difference is not trivial, as it is a claimed limitation.

In addition to these shortcomings, Jardieu's assay does not employ a labeled ligand. The rejected claims recite a "method of detecting and/or quantifying an IgE antibody specific to a ligand." Thus, the ligand is identified based on the ability of an IgE antibody to specifically bind to it. In addition to the unlabeled IgE variant sample, Jardieu's method also uses a labeled normal (non-variant) IgE antibody. This antibody is not part of the sample, but is a reagent used to indirectly detect whether the variant IgE in the sample binds to the receptors and/or the anti-IgE MaE11 antibody. In Jardieu's assay, each of the IgEs used, the unlabeled variant IgE or the labeled normal IgE, bind to the receptors immobilized to the well. There is no teaching in Jardieu to suggest that the variant IgE antibodies tested in Example 5 are anti-IgE antibodies that could bind to the labeled normal IgE antibody in the assay. Thus, Jardieu's assay does not include any ligand that is bound by the variable regions of these variant IgE antibodies, let alone a labeled ligand.

Second, even if the Office's interpretation of Jardieu were correct, it still does not anticipate claims 1-5, 8, 10-12, and 21-23 because it detects an IgG antibody. In the

Office's construction of Jardieu's assay, the sample comprises the MaE11 antibody (anti-IgE) and a reference murine MaE11 monoclonal antibody while the alleged "ligand" is the biotintylated normal IgE. If this were true, Jardieu's assay would be detecting an IgG antibody and not an IgE antibody as recited in the rejected claims. While the labeled biotintylated IgE antibody may serve as a ligand for the anti-IgE MaE11 antibody, the MaE11 antibody itself is not an IgE antibody. MaE11 is an *IgG* antibody that binds to IgE antibodies. See Jardieu at col. 28, lines 16-19 and lines 41-43. Moreover, because MaE11 is an IgG antibody, it would not bind to the IgE receptors that coat the wells of the plate. The Office's designation of MaE11 as the sample in Jardieu's assay results in an inoperative assay. In sum, the Office's construction of Jardieu's assay, even if it could work, which it can't, describes the detection of an IgG antibody (MaE11) and not the detection of an IgE antibody as the claims describe. For this reason as well, Jardieu does not anticipate claims 1-5, 8, 10-12, and 21-23.

Finally, Applicants also disagree with the Office's application of Jardieu to claims 8 and 10. Claim 8 recites "wherein the label compound is a chemiluminescent compound covalently bound to . . . streptavidin." Jardieu's assay uses streptavidin-HRP. See col. 42, line 17. Horseradish peroxidase (HRP) is not a chemiluminescent compound as suggested by the Office, it is an enzyme. Accordingly Jardieu's assay does not teach a chemiluminescent compound covalently bound to streptavidin. Claim 10 recites a ligand bound to biotin or a derivative thereof. As Applicants explained above, Jardieu's assay does not use an IgE ligand and if one were to consider the biotintylated IgE antibody of Jardieu as a ligand, which is incorrect, then the antibody to be detected (MaE11) would be an IgG antibody.

Regarding claim 15, it is unclear to Applicants why the Office attempted to apply Jardieu to this claim at all when it is not among the claims listed in this rejection. See Office Action at page 3. To facilitate prosecution, Applicants address claim 15. As discussed above, Jardieu does not teach a "method for detecting and/or quantifying an IgE antibody specific to a ligand" comprising the steps of "contacting . . . the sample with . . . a free dissolved ligand."

In sum, Jardieu's method does not teach a label that "is associated with the ligand or the IgE antibody," "a free dissolved labeled ligand," or a "ligand [that is] bound to a label compound" as recited in the rejected claims. Moreover, because Jardieu does not use a ligand at all, this reference does not teach the step of "contacting ... the sample with ... a free dissolved ligand" as recited in the rejected independent claims. Lastly, Jardieu does teach that the low affinity, CD23 IgE receptor could be used to detect and quantify the amount of ligand-specific IgE in a sample. Thus, Jardieu cannot anticipate claims 1-5, 8, 10-12, and 21-23. For the reasons provided above, claims 1-5, 8, 10-12, and 21-23 are not anticipated by Jardieu. Applicants therefore request that the Office withdraw this rejection.

Rejections Under 35 U.S.C. § 103

Claims 6, 16, and 17-20 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jardieu in view of U.S. Patent 6,004,745 ("Arnold"). Office Action at page 4. Applying Jardieu as discussed above, the Office acknowledges that this reference does not teach a separation step before adding labels to remove unbound carriers or the number of ligand molecules recited in claim 16. *Id.* Turning to Arnold to remedy the shortcomings of Jardieu, the Office contends that Arnold teaches "a typical sandwich

assay [involving] incubating an immobilized antibody (IgE receptor) with a test medium (sample)." *Id.* at 5. According to the Office, after incubation of the immobilized antibody and the sample, unbound antigen is removed in a separation step followed by incubation with a labeled antibody and a second separation step. *Id.*

Applying these references, the Office contends that it would have been obvious to perform a separation step to remove unbound carrier before adding labels in addition to the separation step to remove unbound label as allegedly taught in Arnold using the reagents in the method of Jardieu. Such a separation step, the Office contends, "increases the sensitivity" of the assay and reduce cross-reactivity between the label and the immobilized antibody. *Id.* Regarding claim 16, the Office also believes that it would have been obvious to use enough ligand molecules to optimize binding of all the IgE molecules "[i]n order to detect all of the IgE present" in a sample. *Id.* Applicants disagree.

As Applicants explained above, Jardieu does not teach a label that is associated with a ligand or the IgE antibody in a sample It does not teach the use of a ligand in its assay at all. Accordingly, Jardieu cannot teach a method for quantifying or detecting an IgE specific to a ligand. Applying the alleged teachings in Arnold pointed to by the Office does not remedy this defect in Jardieu. Arnold does not even mention the detection of IgE, let alone detection of IgE that is specific to a ligand. In addition, the teaching in Arnold that the Office points to describes using an antibody to bind to antibodies in the sample and not the low affinity IgE receptor, CD23. Applicants emphasize that the teaching of an antibody to capture an test antibody in a sample is quite different from using an antibody receptor to capture the test antibody.

If anything, Arnold's invention focuses on developing a method that will increase sensitivity over "heterogeneous" assays, like the one the Office points to, by developing a "homogenous" assay. *See* col. 2, lines 14-16. "Homogenous" assays use a label that can undergo a detectable change in stability whenever a ligand binds to the labeled molecule. *See* col. 4, lines 37-41. As such, these "homogenous" assays do not require any separation steps. *See* col. 1, lines 51-52. Thus, because Arnold teaches towards methods of detecting that do not employ any separation steps, this reference teaches away from the claimed methods, which do employ at least one separation step. Indeed, Arnold's discussion of a two-separation step assay is in the background section of the patent to describe the negative features of the prior assay methods that Arnold's invention seeks to overcome.

Lastly, there is no teaching in either reference that suggests to one of ordinary skill in the art that the low affinity IgE receptor alone should be used in an IgE detection/quantitation assay. As Applicants noted in the prior response, one of ordinary skill in the art, wanting to detect as many IgE antibodies in a sample as possible, would consider the high affinity IgE receptor for detection and not the low affinity receptor. Even the Office's alleged grounds for obviousness are based on increased sensitivity of the assay and detecting all IgE in a sample. If these were the skilled artisan's motivations for combining these references, that same reasoning would guide the skilled artisan away from using the low affinity CD23 IgE receptor for a detection/quantification assay. For these reasons, Applicants respectfully request that the Office withdraw its rejection of claims 6, 16, and 17-20 as obvious.

Claims 9 and 12-14 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jardieu in view of U.S. Patent 6,087,188 ("Johansen"). Office Action at page 6. The Office applies Jardieu as described in the previous section and turns to Johansen for an alleged teaching of an acridinium label, simultaneous incubation of the ligand, sample IgE, and receptor, and the use of a paramagnetic carrier particle. *Id.* According to the Office, it would have been obvious to modify the assay of Jardieu with the use of magnetic particles as carriers and acridinium labels in a simultaneous operation as allegedly taught in Johansen because Johansen teaches that results can be obtained in 15 minutes with such an assay as compared to an ELISA, which takes 2 hours. *Id.* at 8. Applicants traverse.

For the reasons asserted above, Jardieu does not teach the claimed method format. Adding Johansen to Jardieu does not remedy this defect. Like Arnold, Johansen does not teach the use of the low affinity receptor, CD23, in a method of detecting and/or quantifying an IgE antibody. Rather, Johansen uses anti-IgE antibodies. Neither Jardieu nor Johansen suggest the use of CD23 alone in a method of detecting and/or quantifying an IgE antibody specific to a ligand as recited in independent claim 1. Thus, the combination of these references cannot render dependent claims 9 and 12-14 obvious. Applicants therefore respectfully request that this rejection be withdrawn.

Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the claims 1-6 and 8-23.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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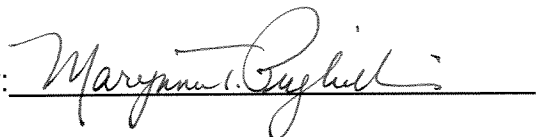
Dated: March 27, 2008

By: 

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